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REVIEW ARTICLE

# Inflammaging: Mechanisms, Therapeutic Strategies, and Implications for Age-Related Diseases

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## ABSTRACT

**Purpose:** This review synthesizes current mechanistic understanding of inflammaging pathophysiology, with particular emphasis on cellular senescence, mitochondrial dysfunction, and aberrant innate immune regulation. Furthermore, it evaluates novel therapeutic modalities targeting these molecular pathways and examines their clinical relevance for cardiovascular pathology, neurodegenerative conditions, metabolic disorders, and oncological diseases.

**Materials and Methods:** A comprehensive narrative review was conducted examining primary literature from 2000 to 2025, focusing on molecular mechanisms including senescence-associated secretory phenotype (SASP), mitochondrial damage-associated molecular patterns (mtDAMPs), and macrophage polarization dynamics. Therapeutic interventions were evaluated based on preclinical and clinical evidence, including senolytic compounds, metabolic interventions, and biologic agents.

**Results:** Cellular senescence drives inflammaging through the SASP, wherein senescent cells secrete pro-inflammatory cytokines, chemokines, and proteolytic enzymes via NF-κB, C/EBPβ, and mTOR signaling cascades. Mitochondrial deterioration releases mtDAMPs and reactive oxygen species, activating NLRP3 inflammasome and cGAS-STING pathways. Macrophage functional reprogramming toward pro-inflammatory phenotypes amplifies these responses. Clinically, elevated inflammatory biomarkers predict morbidity and mortality in aging populations, with the CANTOS trial establishing causality between IL-1β-mediated inflammation and cardiovascular events. Therapeutic strategies demonstrate promise: senolytics (fisetin, dasatinib/quercetin) selectively eliminate senescent cells; mTOR inhibitors modulate SASP; metabolic interventions including caloric restriction improve immune cell function; and targeted biologics reduce systemic inflammation.

**Conclusion:** Inflammaging represents a fundamental biological process bridging cellular senescence to systemic disease pathology. The intricate interplay among senescent cells, mitochondrial impairment, innate immune dysregulation, and chronic low-grade inflammation establishes the pathological foundation underlying major age-related diseases. Emerging therapeutic approaches including senolytics, metabolic interventions, and precision biologics demonstrate considerable potential for healthspan extension and reduction of age-associated disease burden. Future investigations must refine intervention protocols, establish optimal timing for therapeutic initiation, develop comprehensive biomarker panels, and implement precision medicine strategies in geroscience. (*Open J Biomed Res 2025;4:18-23*)

## Keywords

Inflammaging, Cellular senescence, Senescence-associated secretory phenotype, Senolytics, Age-related diseases.

## AUDIOABSTRACT

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## INTRODUCTION

The global demographic shift toward aging populations has intensified scientific investigation into the biological mechanisms governing senescence. Among the diverse hallmarks characterizing aging, persistent low-grade inflammation has emerged as a critical nexus connecting cellular aging to systemic disease manifestation.[1] Originally conceptualized by Franceschi and colleagues, the term "inflammaging" describes the progressive development of a pro-inflammatory milieu that intensifies with advancing chronological age.[2] Epidemiological studies have consistently demonstrated that elevated inflammatory biomarkers serve as independent predictors of morbidity and mortality among older adults, even after controlling for established risk factors.[3] This sustained inflammatory tone contributes substantially to the initiation and progression of multiple age-related conditions,

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encompassing cardiovascular disease, type 2 diabetes mellitus, neurodegenerative disorders, and specific malignancies.[4] Consequently, elucidating the molecular foundations of inflammaging has become essential for developing targeted interventions that promote healthy aging trajectories.

## MOLECULAR MECHANISMS UNDERLYING INFLAMMAGING

### *Cellular Senescence and the Senescence-Associated Secretory Phenotype*

A principal driver of inflammaging is cellular senescence a terminal state wherein cells undergo irreversible growth arrest in response to telomere attrition, DNA damage accumulation, and various cellular stressors.[5] Rather than remaining metabolically quiescent, senescent cells acquire the senescence-associated secretory phenotype (SASP), characterized by active release of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α), chemokines, growth factors, and matrix-degrading proteases.[1] The SASP reinforces senescence through autocrine signaling loops while simultaneously inducing paracrine inflammation in neighboring cells and distal tissues throughout the organism.[5] Critical molecular regulators of SASP induction include nuclear factor-kappa B (NF-κB), CCAAT/enhancer-binding protein beta (C/EBPβ), and mammalian target of rapamycin (mTOR) signaling networks, which integrate diverse stress signals and drive transcription of inflammatory mediators.[1] The progressive accumulation of SASP-secreting senescent cells has been implicated in osteoarthritis pathogenesis, atherosclerotic plaque development, neurodegenerative processes, and tumorigenesis, rendering selective elimination of these cells an appealing therapeutic objective.[6]

### *Mitochondrial Dysfunction and Damage-Associated Molecular Patterns*

Mitochondria function as central regulators of cellular metabolism and innate immune signaling transduction.[7] With advancing age, mitochondrial function deteriorates progressively, manifesting as compromised oxidative phosphorylation efficiency, enhanced reactive oxygen species (ROS) generation, and release of mitochondrial damage-associated molecular patterns (mtDAMPs) including mitochondrial DNA (mtDNA) and cardiolipin.[1] Dysfunctional mitochondria discharge mtDAMPs and ROS that activate innate immune sensors, particularly the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome.[8] This multiprotein complex facilitates the proteolytic maturation of pro-inflammatory cytokines IL-1β and IL-18 through caspase-1 activation.[9] Compromised mitophagy the selective autophagic degradation of damaged mitochondria amplifies this inflammatory cascade, resulting in the accumulation of dysfunctional mitochondria and establishing a self-perpetuating cycle of chronic inflammation.[10] The cGAS-STING and NF-κB pathways intersect with mitochondrial dysfunction, further intensifying inflammatory responses and contributing to cardiovascular, neurodegenerative, and metabolic pathologies.[1]

### *Macrophage Polarization and Innate Immune Dysregulation*

Macrophages serve as pivotal orchestrators of innate immunity and are critically involved in both the initiation and resolution of inflammatory responses.[11] During inflammaging, macrophages undergo functional reprogramming characterized by low-level activation and altered polarization profiles. Aging compromises macrophage polarization dynamics, frequently biasing toward a pro-inflammatory phenotype with enhanced basal secretion of IL-1β, TNF-α, IL-6, and chemokines CXCL9 and CXCL10, even in the absence of explicit stimulation.[1] This age-related phenotypic shift is partially driven by mitochondrial dysfunction, notably diminished mitochondrial calcium uptake capacity, which amplifies cytosolic calcium signaling and activates the NF-κB pathway.[7] Consequently, aged macrophages become hyper-responsive to inflammatory stimuli and predisposed to chronic inflammatory output. The NLRP3 inflammasome is additionally upregulated with age, primed by NF-κB and activated by mitochondrial ROS, leading to caspase-1-dependent maturation of IL-1β and IL-18 and pyroptotic cell death.[10] Furthermore, aged macrophages exhibit diminished efferocytosis the clearance of apoptotic cells and impaired tissue repair capabilities, resulting in the accumulation of apoptotic cells and DAMPs that perpetuate chronic inflammation.[1]

## SYSTEMIC BIOMARKERS OF INFLAMMAGING

Characterization of inflammaging depends substantially upon quantifiable biomarkers. Longitudinal investigations have identified several key inflammatory mediators that increase with age, including IL-6, IL-1 receptor antagonist protein (IL-1RN), IL-8, IL-18, CRP, interferons (IFN-α, IFN-β),

transforming growth factor-beta (TGF-β), TNF-α, and soluble TNF receptors.[12] Among these, IL-6 has garnered particular attention due to its robust associations with aging and adverse health outcomes. Research indicates that IL-6 concentrations, typically low or undetectable in healthy adults, become elevated in older individuals, with progressively increasing concentrations observed in the very old.[13] Similarly, CRP and TNF-α demonstrate age-dependent elevations and have been associated with disability, frailty, and mortality in aging populations.[14] Notably, studies of healthy aging reveal that while pro-inflammatory cytokine levels are higher in older adults compared to younger populations, they generally remain within clinically normal ranges, suggesting that inflammaging represents a shift in baseline immune homeostasis rather than pathological inflammation per se.[3] This observation has prompted suggestions that normal reference ranges for inflammatory markers may require age-specific adjustment.[15]

## INFLAMMAGING IN AGE-RELATED DISEASES

### *Cardiovascular Disease and Atherosclerosis*

Atherosclerosis exemplifies the pathological consequences of inflammaging, representing a chronic inflammatory disease of the arterial wall.[16] The pathophysiology involves the retention and oxidation of low-density lipoprotein (LDL) in the subendothelial space, triggering monocyte recruitment and differentiation into macrophages.[17] Within the plaque microenvironment, macrophages adopt pro-inflammatory M1 phenotypes, releasing cytokines that promote plaque inflammation and progression.[18] Hypoxia within advanced plaques activates hypoxia-inducible factor-1 alpha (HIF-1α) and mTORC1 signaling in macrophages, leading to NF-κB activation and sustained inflammatory gene expression.[16] The NLRP3 inflammasome plays a particularly crucial role, with its activation leading to IL-1β and IL-18 release that drives chemotaxis and foam cell formation.[19] Definitive clinical evidence supporting the inflammatory hypothesis of cardiovascular disease emerged from the CANTOS trial, which demonstrated that canakinumab, a monoclonal antibody targeting IL-1β, significantly reduced cardiovascular events independent of lipid-lowering effects.[19] This landmark study established inflammation as a causal factor in atherosclerosis and validated anti-inflammatory strategies for cardiovascular risk reduction.

### *Neurodegenerative Disorders*

Chronic low-grade inflammation contributes significantly to neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease.[21] Microglia, the resident immune cells of the central nervous system, become primed and hyper-responsive with age, releasing pro-inflammatory cytokines that promote neuronal dysfunction and death. The NLRP3 inflammasome has been implicated in Alzheimer's pathogenesis, with activation driving neuroinflammation and amyloid-beta-induced neurotoxicity.[10]

### *Metabolic Syndrome and Type 2 Diabetes*

Inflammaging closely intertwines with metabolic dysfunction.[15] Adipose tissue, particularly visceral fat, serves as a major source of pro-inflammatory adipokines including IL-6, TNF-α, and leptin, while anti-inflammatory adiponectin levels decline with age and obesity.[21] Macrophage infiltration into adipose tissue increases with aging, with a phenotypic shift from anti-inflammatory M2 to pro-inflammatory M1 macrophages exacerbating insulin resistance and metabolic dysregulation.[6] Advanced glycation end-products (AGEs), formed through dietary intake and endogenous production, accumulate with age and bind to the receptor for AGEs (RAGE), triggering NF-κB-mediated pro-inflammatory cytokine transcription and contributing to vascular complications.[22]

### *Cancer*

The intersection of inflammaging and cancer involves multiple mechanisms.[22] Chronic inflammation creates a microenvironment conducive to malignant transformation, tumor promotion, and metastasis. Senescent cells within the tumor microenvironment secrete SASP factors that can promote tumor growth and immune evasion. Additionally, age-associated B cells (ABCs), which accumulate in aging individuals, secrete elevated levels of IL-6, TNF-α, and autoantibodies, perpetuating inflammation and potentially contributing to hematologic malignancies.[6]

## SEX DIFFERENCES IN INFLAMMAGING

Emerging evidence highlights significant sex differences in inflammaging trajectories.[12] Premenopausal women generally exhibit lower baseline inflammatory markers and more robust adaptive immune responses compared to age-matched men. However, following menopause, women demonstrate elevated IL-6 levels and altered

inflammatory profiles that converge with or exceed those of men.[12] Postmenopausal women exhibit higher IL-6 levels (approximately 5.2 pg/mL) compared to premenopausal women (2.6 pg/mL), with estrogen deprivation enhancing IL-6 production from peripheral blood mononuclear cells.[12] These observations suggest that sex hormones, particularly estrogen, modulate inflammaging processes and may partially explain the differential prevalence of autoimmune and inflammatory diseases between sexes.

## THERAPEUTIC STRATEGIES TARGETING INFLAMMAGING

### *Senolytic and Senomorphic Approaches*

Senolytic therapies, which selectively eliminate senescent cells, represent a promising strategy for mitigating inflammaging.[6] Small-molecule senolytics including fisetin, a natural flavonoid, and navitoclax (ABT263), a BCL-2 family inhibitor, have demonstrated efficacy in preclinical models by clearing senescent cells and reducing SASP-driven inflammation.[6] The combination of dasatinib and quercetin has shown promise in early clinical trials, improving physical function and reducing senescence markers in patients with idiopathic pulmonary fibrosis.[6] Intermittent high-dose fisetin regimens have been tested in osteoarthritis, frailty, and cardiovascular disease populations, demonstrating enhanced physical function and decreased circulating SASP factors including IL-6 and CRP, though effects vary by disease subtype and baseline senescence burden [6]. Senomorphic approaches, which suppress SASP without eliminating senescent cells, offer alternative strategies. JAK/STAT inhibitors such as ruxolitinib directly modulate SASP production, alleviating chronic inflammation and improving tissue integrity.[6]

### *mTOR Inhibition*

The mTOR pathway integrates nutrient sensing with cellular metabolism and inflammatory responses.[1] mTOR inhibitors, particularly rapamycin and its analogs, reduce pro-inflammatory activity and promote tissue regeneration by regulating SASP components such as IL-1α. These compounds have demonstrated lifespan extension in model organisms and are currently under investigation for their potential to modulate human aging.[6]

### *NLRP3 Inflammasome Inhibition*

Given the central role of NLRP3 inflammasome activation in inflammaging, targeted inhibition of this pathway has garnered significant interest.[10] MCC950 and other small-molecule inhibitors have shown efficacy in preclinical models of inflammatory diseases, though clinical translation requires careful consideration of infection risks associated with broad inflammasome suppression.[1]

### *Metabolic Interventions*

Caloric restriction and intermittent fasting trigger metabolic rewiring in immune cells, improving mitochondrial efficiency and autophagy while preserving naïve T-cell pools and reducing systemic pro-inflammatory cytokine levels.[6] Plant-based diets rich in fiber promote the production of short-chain fatty acids (SCFAs) through gut microbial fermentation. Butyrate, in particular, enhances regulatory T-cell differentiation, suppresses pro-inflammatory cytokine production, and modulates gene expression via histone deacetylase inhibition.[15]

### *Anti-Inflammatory Biologics*

Beyond cardiovascular applications, anti-inflammatory biologics show promise for other age-related conditions. Recent meta-analyses indicate that anti-inflammatory interventions, including omega-3 fatty acids and botanical compounds, demonstrate moderate beneficial effects for depression treatment in older adults, highlighting the systemic impact of inflammaging on mental health.[23]

## FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

The recognition of inflammaging as a fundamental aging process has profound implications for clinical practice and drug development.[24] Several key considerations emerge from the current evidence base: First, the heterogeneity of inflammaging among individuals necessitates personalized approaches to anti-inflammatory interventions. Baseline inflammatory status, genetic factors, and comorbidity profiles likely influence treatment responses, requiring stratified medicine approaches in clinical trials.[23] Second, biomarker development must advance beyond crude measures such as CRP and IL-6 to encompass multi-omic signatures that capture the complexity of immune aging.[24] Such approaches would enable better risk stratification and monitoring of therapeutic efficacy. Third, the timing of interventions may prove critical. Preventive strategies

initiated during middle age, before the establishment of irreversible organ damage, may yield greater benefits than treatment initiated in advanced age.[6] Finally, combination approaches targeting multiple hallmarks of aging simultaneously senolytics combined with metabolic interventions, for example may prove more effective than single-target strategies.[1]

## DISCUSION

The findings of this review highlight that inflammaging is not merely a passive consequence of growing older, but rather an active, modifiable driver of age-related diseases. At the cellular level, the accumulation of senescent cells and their secretory phenotype (SASP) emerges as a primary instigator, releasing pro-inflammatory signals that propagate through tissues via NF-κB and mTOR pathways.[1,5] What makes this in particular significant is that these mechanisms are now clinically actionable. The CANTOS trial demonstrated that targeting IL-1β with canakinumab reduces cardiovascular events independent of cholesterol levels, providing the first definitive evidence that inflammation itself is a causal factor in atherosclerosis.[19] This paradigm shift positions chronic low-grade inflammation as a legitimate therapeutic target, much like hypertension or hyperlipidemia, rather than an irreversible aspect of aging.

Translating these mechanistic insights into patient care, however, requires navigating the complexity of human heterogeneity. Senolytic therapies compounds that selectively eliminate senescent cells have shown remarkable promise in preclinical models and early human trials. The dasatinib-quercetin combination, for instance, improves physical function and reduces circulating inflammatory markers in patients with idiopathic pulmonary fibrosis.[6] Yet, the field faces practical challenges: optimal dosing schedules remain uncertain, long-term safety profiles require clarification, and the question of when to initiate therapy before or after organ damage becomes established lacks definitive answers.[6,24] Moreover, sex-specific differences in inflammatory trajectories, in particular the elevation of IL-6 following menopause, suggest that therapeutic approaches may need tailoring beyond one-size-fits-all protocols.[12] These considerations underscore the necessity of biomarker-guided, individualized strategies rather than universal prescriptions.

Looking ahead, the most promising avenue may lie in combination interventions that address multiple aging hallmarks simultaneous. While senolytics clear damaged cells, metabolic approaches such as caloric restriction or mTOR inhibition appear to rejuvenate immune cell function and suppress SASP production.[6] Dietary interventions rich in fiber-derived short-chain fatty acids offer accessible, low-risk complements to pharmacological strategies.[15] Ultimate, the goal is not simply lifespan extension but the compression of morbidity ensuring that increased longevity is accompanied by preserved physical and cognitive function. Achieving this will demand refined biomarker panels capable of capturing the nuanced landscape of immune aging, together with clinical trials that stratify participants by baseline inflammatory status, genetic risk, and comorbidity profiles.[24] As the field matures from mechanistic discovery to precision therapeutics, inflammaging stands poised to transform geriatric medicine from reactive symptom management to proactive biological intervention.

## CONCLUSION

Inflammaging represents a fundamental biological process linking cellular senescence to systemic disease. The complex interplay between senescent cells, mitochondrial dysfunction, innate immune dysregulation, and chronic low-grade inflammation creates a pathological milieu that underlies the major diseases of aging. While significant challenges remain in translating mechanistic insights into clinical practice, emerging therapeutic strategies including senolytics, metabolic interventions, and targeted biologics offer promise for extending healthspan and reducing the burden of age-related disease. Future research must focus on refining these interventions, identifying optimal timing and patient selection criteria, and developing comprehensive biomarker panels to guide precision medicine approaches in geroscience.

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